Disseminated Intravascular Coagulation: *
A Cause of Shock

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THE CAUSES of shock have been the subject of intensive research for many years, and numerous factors have been shown to be associated with the onset of shock. Some of these include loss of blood volume due to fluid or whole blood loss, vasodilation of peripheral or splanchnic bed, tissue trauma, anaphylaxis, reflex vasodilation and others. This paper represents an attempt to demonstrate that certain types of shock are due specificially to intravascular clotting.

Many examples of the association of shock and disseminated intravascular coagulation may be found in patients with certain specific disease entities. The association has been pointed out in patients with a) infantile diarrhea due to *B. coli*,[9] b) pseudomembranous enterocolitis,[5] c) premature separation of the placenta and eclampsia,[7] d) amniotic fluid embolization,[3] and e) incompatible blood transfusion reaction.[4]

The same association has been noted in animal experiments. In 1944 Mirsky and Freis [10] injected trypsin intravenously into rats and rabbits and produced a fatal circulatory collapse. They found extensive intravascular clotting in the heart and lungs when the trypsin was injected in high concentrations, and in the liver and kidneys when it was injected in dilute repeated doses.

It was observed in 1955 [9] in experiments which resulted in disseminated intravascular coagulation that the formation of thrombi was accompanied by a state of hypotension and shock which under certain experimental conditions was irreversible and resulted in the death of the animal in a few hours. The thrombi were produced by injection of incompatible (human) blood and occurred in a variety of organs under various experimental conditions.[4, 6]

While the association of shock and intravascular clotting is clear and unmistakable the problem of which comes first remains to be settled. Crowell's experiments [2] shed some light on the situation with respect to the shock associated with blood volume depletion and cardiac arrest. He produced cardiac arrest (and absent blood pressure) in dogs by first causing ventricular fibrillation. After cardiac arrest of three minutes the heart was started again, but a fatal outcome was the usual result. At autopsy of these animals, small blood clots were demonstrated in the pulmonary vessels. It was then shown that the survival rate of the dogs could be approximately doubled if the animals were previously heparinized to prevent the formation of the clots.

Subsequently Crowell's group [1] produced a controlled steady state of shock, lowering the blood pressure to 50 mm. of Hg for 90 minutes and 30 mm. of Hg. for 45 minutes,

* Submitted for publication June 17, 1958.

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by bleeding the dogs into a reservoir containing citrate as the anticoagulant. A marked shortening of the whole blood coagulation time was found during the period of shock. When the animal's own blood was re-injected into its circulation, the blood pressure tended to rise to normal levels but subsequently dropped, and after several hours the dogs expired. Small blood clots were demonstrated in the pulmonary vessels by washing them out by reverse perfusion. Heparin was used just before death to prevent postmortem clotting.

Crowell was able to prevent death in nearly all dogs under the same experimental conditions if heparin were administered prior to the development of shock. On the other hand when heparin was mixed with the blood in the reservoir it did not prevent irreversible shock. These experiments indicate that pulmonary thrombi are responsible for irreversible shock and death but also suggest that the thrombi are the result of the shock, apparently participating in a vicious circle.

The injection of incompatible blood and amniotic fluid results in shock and intravascular thrombi. The shock is usually reversible and obviously originates in a manner different from the experiments of Crowell. It was the object of the experiments reported herein to determine whether heparin would prevent hypotension from these two agents and thus to assess the role of intravascular clotting in the pathogenesis of this type of shock.

Materials and Methods

Mongrel dogs of both sexes were anesthetized by intravenous sodium pentobarbital, 5 mg./Kg. of body weight. Two polyethylene catheters were placed in the aorta by way of each femoral artery so that the tip of each lay at the level of the diaphragm. One was connected to a mercury manometer to measure aortic blood pressure. The other was used for the injection

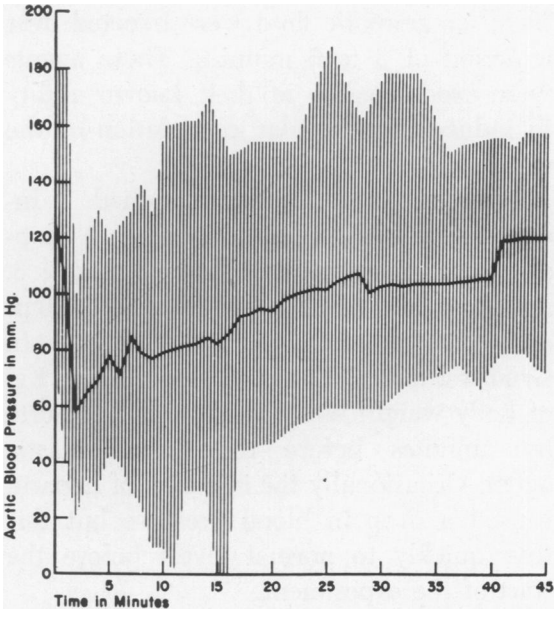

FIG. 1. Incompatible blood transfusion.

of incompatible blood, amniotic fluid or heparin. A laparotomy was then done. One kidney was dissected free of surrounding tissue except for its pedicle and kidney biopsies taken every 15 minutes.* Portal pressures were measured from a splenic vein with a water manometer. On one dog a catheter was inserted into the right pulmonary artery by way of the right external jugular vein. Pressure studies were recorded on a Hellgi Multiscriptor and a Mueller pressure amplifier and transducer.** The superior mesenteric artery was occluded during the injection of incompatible blood and amniotic fluid. This was done because in previous experiments when the superior mesenteric artery was not occluded during the injection of incompatible blood, pseudomembranous enteritis developed and the dogs died of irreversible shock.[5] One hundred ml. of incompatible

* The kidney studies will be reported in a subsequent paper.

** We wish to express appreciation to Col. Weldon J. Walker, Cardiology Consultant for the United States Army in Europe, for carrying out the cardiac catheterization.

blood or amniotic fluid were injected over a period of 3 to 5 minutes. These agents were used because of their known ability to induce intravascular coagulation of the disseminated type.

Four groups of dogs were studied; 1. Incompatible blood alone (22 dogs); 2. Heparin plus incompatible blood (6 dogs); 3. Amniotic fluid alone (4 dogs), and 4. Heparin plus amniotic fluid (4 dogs). In Groups 2 and 4, 10 mg. of heparin per Kg. of body weight was injected into the aorta ten minutes before the thromboplastic agent. Occasionally the injection of heparin caused a drop in blood pressure but this rose quickly to normal levels before the start of the experiment.

Results

Group 1: The injection of incompatible blood into the aorta at the level of the diaphragm caused an immediate precipitous fall in blood pressure to shock levels (Fig. 1). Death occurred in a few cases but most of the animals survived. In the majority the blood pressure leveled off at a range of 20 to 50 mm. of Hg and began a slow climb toward normal which was usually reached within one hour. The average drop in this group was 84.4 mm. of Hg. Splenic vein pressure determinations were made on ten dogs immediately before and immediately after blood transfusion without heparin with the following results.

Splenic Vein Pressure in Cm. H_2O

Dog	Before Transfusion	After Transfusion
G–64	9	20
G–65	10.5	37
G–66	7.8	19.5
G–68	10	53
G–69	7.7	18
G–70	5.5	15
G–71	19	20
G–72	4.5	16
G–73	9.5	29
G–75	5.5	14.5
	Average 8.9 cm.	Average 24.2 cm.

The splenic veins were observed to be markedly dilated after the transfusion. At the same time the peripheral veins were completely collapsed. On dog G-77, recordings of the right pulmonary pressure were made with the following results (Fig. 5).

	Mean Systemic Blood Pressure	Mean Pulmonary Artery Pressure
Before transfusion	125 mm. Hg	9.3 mm. Hg
6 Min. after transfusion	50 mm. Hg	17.3 mm. Hg
18 Min. after transfusion	100 mm. Hg	16.0 mm. Hg
27 Min. after transfusion	125 mm. Hg	10.6 mm. Hg
40 Min. after transfusion	125 mm. Hg	9.3 mm. Hg

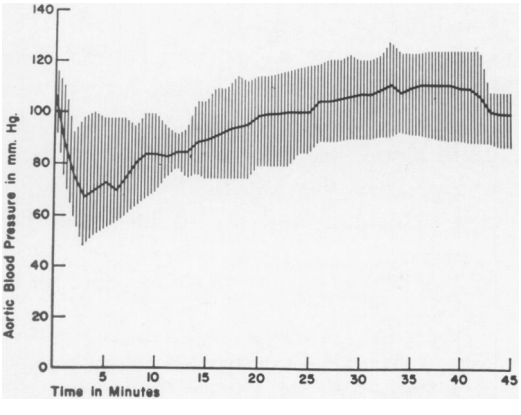

FIG. 2. Incompatible blood plus Heparin.

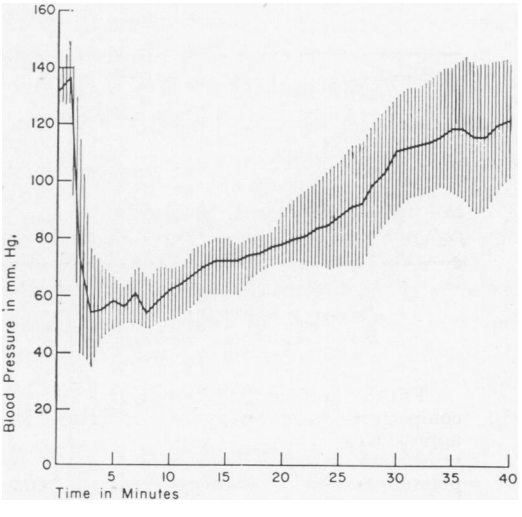

FIG. 3. Amniotic fluid infusion.

The amplitude of the pulmonary artery pulsations was decreased after the transfusion. This probably indicates an increase in pulmonary resistance.

Group 2: When heparin was administered prior to the incompatible blood (Fig. 2) hypotension developed as before, but the drop in blood pressure was not as great. The average fall in blood pressure was 45.5 mm. of Hg as compared with 84.4 mm. in the unheparinized animals.

Group 3: The injection of amniotic fluid into the aorta caused a marked initial drop in blood pressure followed by a gradual rise to normal within 45 minutes to one hour. The average drop was 91.7 mm. of Hg (Fig. 3).

Group 4: Heparinized animals given amniotic fluid had an average drop in systemic blood pressure of 7.3 mm. of Hg (Fig. 4).

While none of the heparinized animals died, three of the unheparinized dogs died immediately of shock. Microscopic examination of these three dogs revealed numerous thrombi in the capillaries and small vessels of the lungs and liver (Fig. 6–10). Surviving animals became apnoeic and cyanotic. After a short period of apnoea they developed hyperpnea which lasted about the same time as the hypotension and cyanosis.

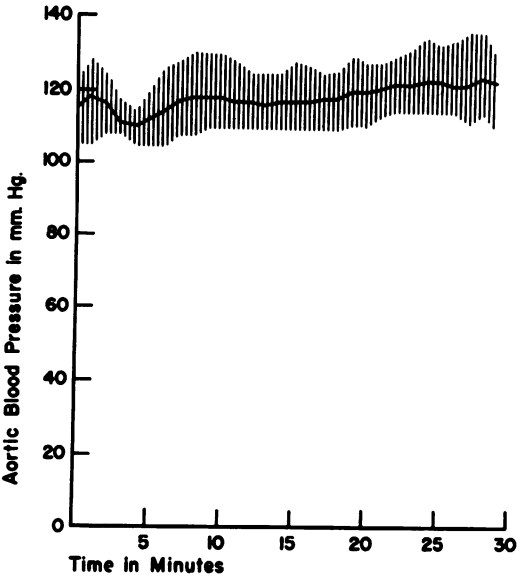

FIG. 4. Amniotic fluid plus heparin.

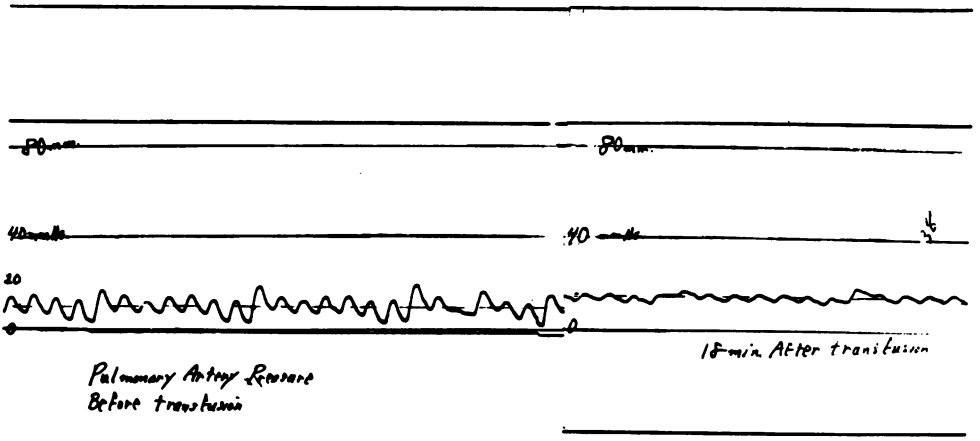

FIG. 5. Recording of pulmonary artery pressure before and 18 minutes following the incompatible transfusion. The incomplete line through the pulse waves was drawn at the approximate mean, and used to measure the mean pressure. It can be seen that before the transfusion the amplitude of the waves is much greater than following it, and the mean pressure is lower. Variations due to respirations are evident in both cases. The pressure both before and after the transfusion is relatively low but the standardization was kept constant throughout the experiment.

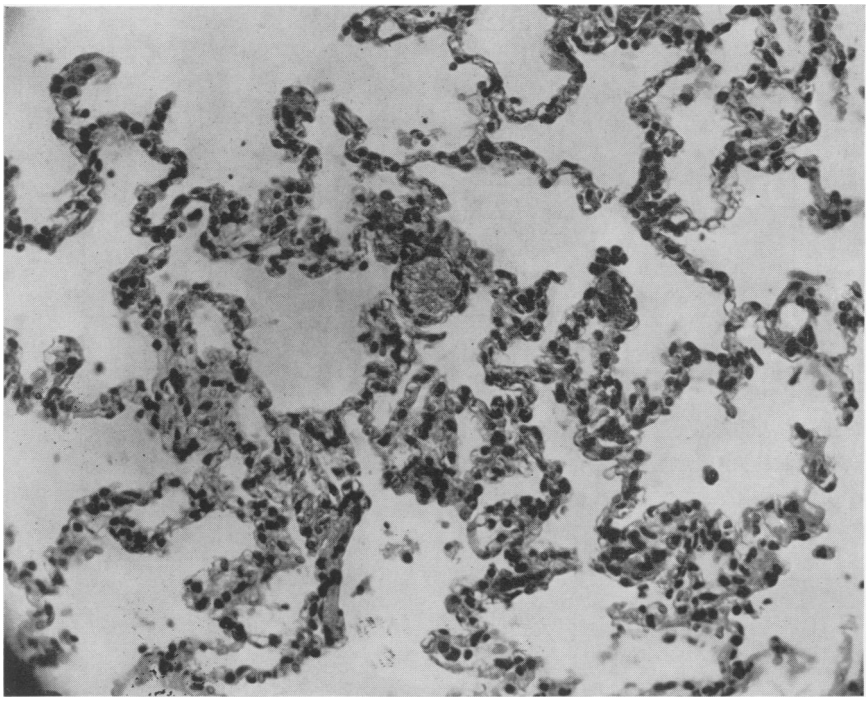

FIG. 6. Lung. Thrombus in pulmonary capillary. Hematoxylin and eosin stain. × 240. (Walter Reed Army Hospital AMH 15250-C.)

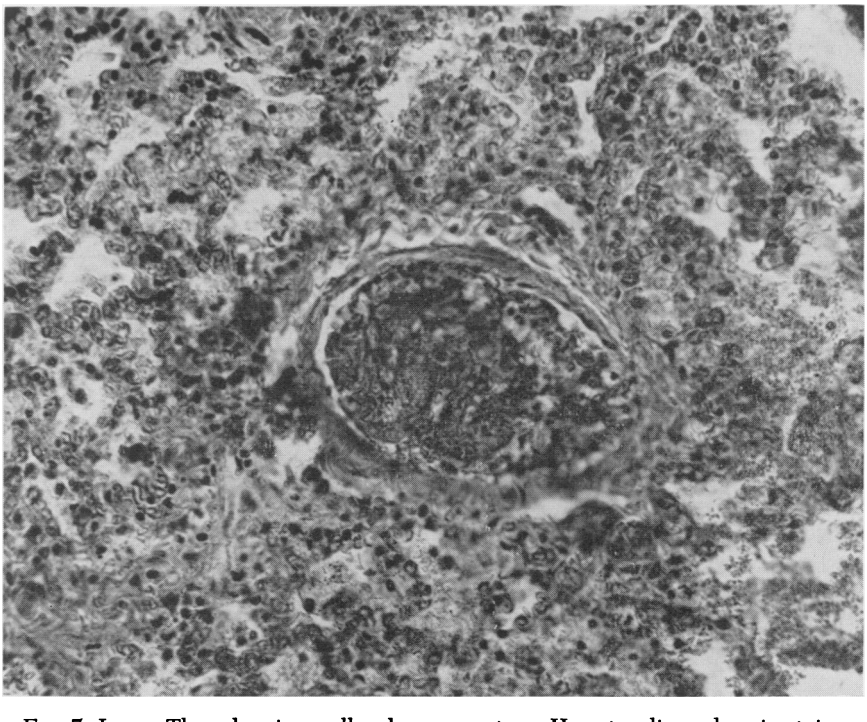

FIG. 7. Lung. Thrombus in small pulmonary artery. Hematoxylin and eosin stain. × 240. (Walter Reed Army Hospital AMH 15250-N.)

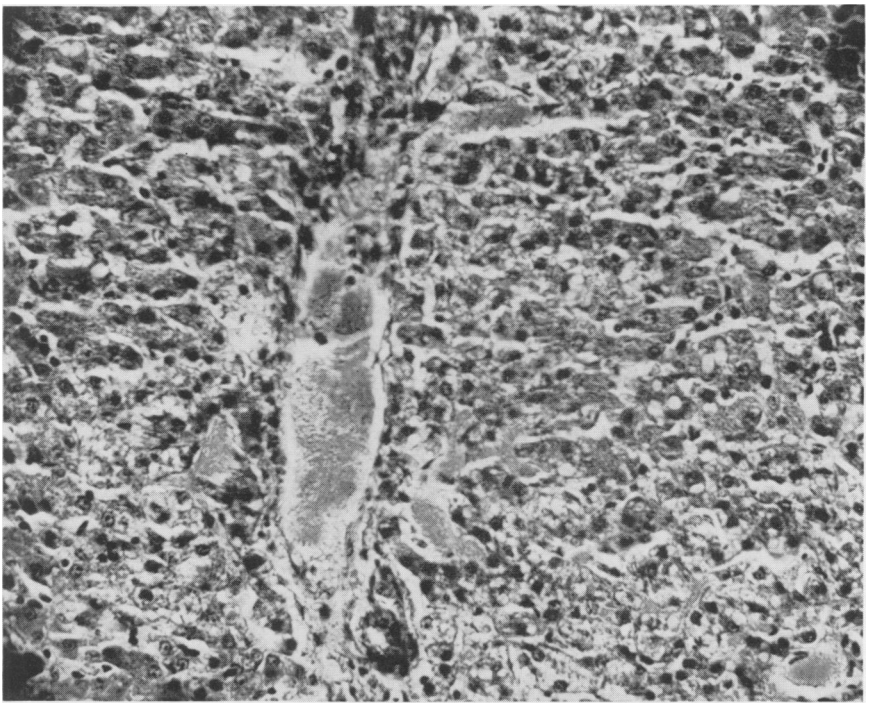

FIG. 8. Liver. Thrombi in hepatic arterioles extending out into sinuses between liver cells after incompatible transfusion in dogs. Hematoxylin and eosin stain. × 240. (Walter Reed Army Hospital AMH 15250-E.)

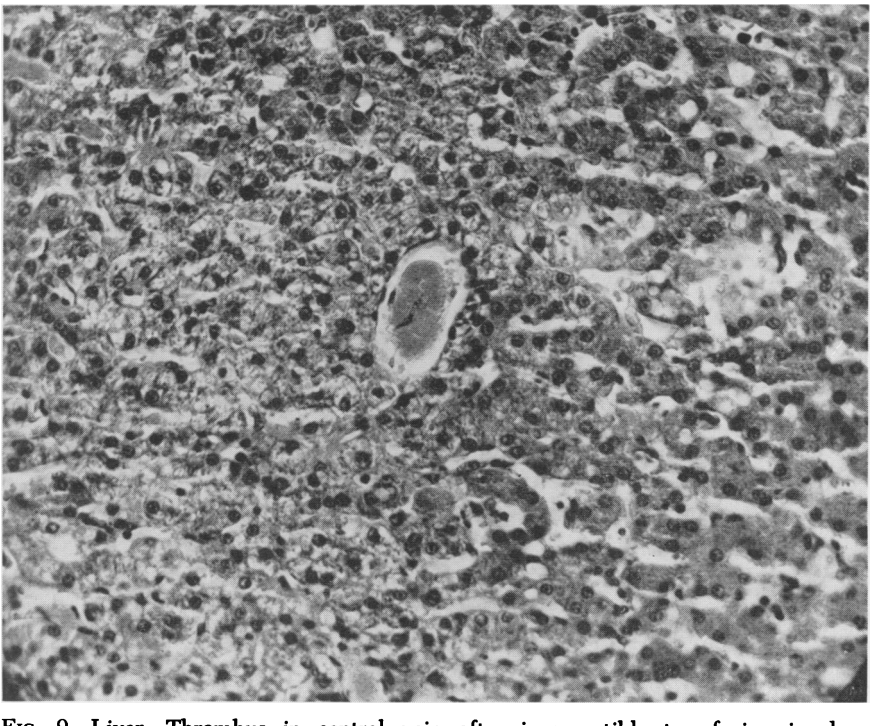

FIG. 9. Liver. Thrombus in central vein after incompatible transfusion in dog. Hematoxylin and eosin stain. × 240. (Walter Reed Army Hospital AMH 15250-D.)

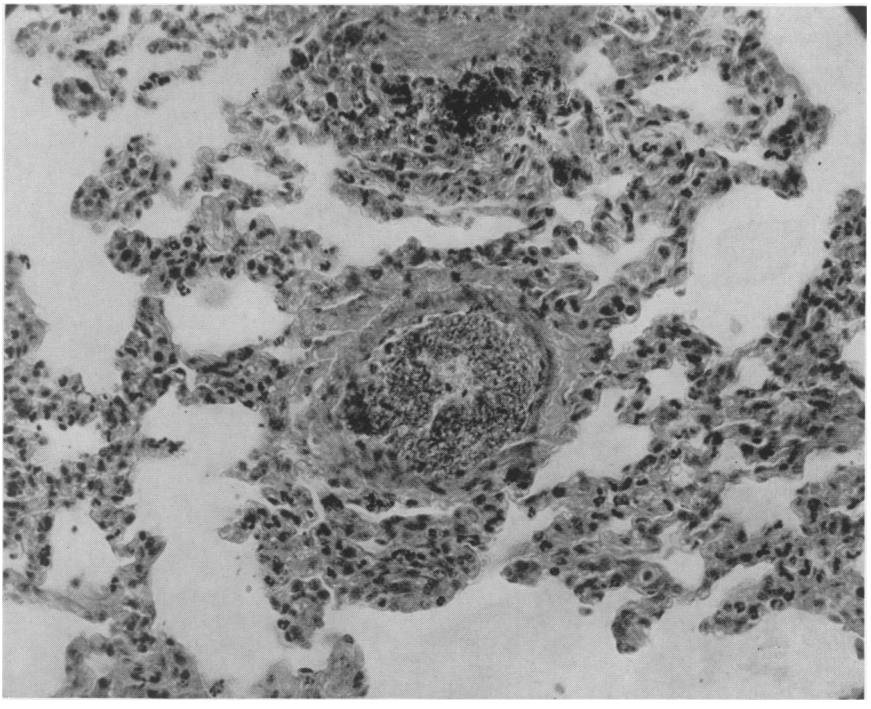

FIG. 10. Lung. Thrombus in small pulmonary artery. Hematoxylin and eosin stain. × 240. (Walter Reed Army Hospital AMH 15250-N.)

Discussion

These experiments show that the shock due to amniotic fluid embolization is prevented by pretreatment with heparin. Therefore they suggest that the major portion of the shock in this condition is due to intravascular coagulation. The degree of shock associated with incompatible blood transfusion was reduced by heparin, indicating that some of the immediate hypotension is due to intravascular clotting, but also that the fall in blood pressure is partially due to some other factor. It may be that temporary obstruction of the small vessels by masses of agglutinated red cells is responsible for this additional drop in blood pressure. We have concluded from these experiments that under these conditions intravascular coagulation may be entirely or partially responsible for *reversible shock*. Crowell [1] demonstrated that intravascular thrombosis may be the cause of certain types of *irreversible shock*. The possibility exists that a vicious cycle may be set up in which shock may be induced by intravascular coagulation and then a prolonged and profound degree of shock may itself produce thrombi which in turn produce and maintain the hypotension to the point of death.

The mechanism of production of hypotension by intravascular thrombosis is unknown. Nevertheless, certain information derived from the experiments of Schneider [11] and Weil [12] indicate several possible mechanisms that deserve further exploration:

a) Decreased cardiac output due to *acute cor pulmonale*. Schneider [11] has demonstrated a fall in the systemic blood pressure, concomitant with a rise in pulmonary artery pressure, when a variety of thromboplastic agents are injected into the venous circulation. At the same time numerous tiny thrombi are formed in the pulmonary vascular bed. It was suggested by Schneider

that this occlusion of the pulmonary blood vessels caused acute cor pulmonale with a decreased return of blood to the left side of the heart, and a decreased cardiac output leading to a drop in the systemic blood pressure. Our observation (in one dog studied) of a moderate increase in pulmonary artery pressure from 9.3 to 17.3 mm. Hg following the intra-aortic transfusion would tend to support this theory. The decrease in amplitude of the pulmonary pulse would indicate also an increase in pulmonary resistance.

b) Decreased cardiac output due to *decreased venous return to the heart.* Weil et al [12] have produced experimental evidence that a decreased venous return due to pooling of blood in the splanchnic bed may be responsible for the shock occurring when bacterial endotoxin is injected into the circulation. They observed a drop in systemic blood pressure after the injection of toxin and noted that the percentage by which the blood pressure decreased was the same as the percentage decrease in cardiac output. By calculation they found that there was no decrease in the peripheral resistance, and by use of a pump which maintained the venous return at a normal rate were unable to produce hypotension with endotoxin. They concluded that the decreased cardiac output was due to a decreased venous return to the heart. Upon measuring the pressure in peripheral veins, vena cava and portal vein, it was found that the venous pressure in the first two locations remained the same or dropped slightly, whereas the pressure in the portal vein increased markedly. Our observation of an average increase in portal pressure from 8.9 cm. to 24.2 cm. would tend to support the theory of damming of blood in the portal system by the liver with resulting decreased venous return to the heart. This fits in with the findings of Weil et al when they concluded that under the influence of bacterial endotoxin the liver provided an obstruction to the return of blood to the heart from the splanchnic system. They considered the mechanism of the obstruction to be a constriction of vessels in the liver, but this may be secondary to actual thrombosis.

This mechanism has been considered in this discussion because bacterial endotoxin is now known to induce intravascular thrombosis.[8] It has been demonstrated both *in vivo* and *in vitro* that endotoxins shorten the coagulation time of blood. *In vivo* it produces a drop in circulating fibrinogen and platelets. Simultaneously with the drop in fibrinogen, microscopic thrombi appear in a variety of organs. After one injection of toxin they are found in the lungs, spleen and in the central veins of the liver. It seems quite likely that these thrombi which provide an organic occlusion of some of the central veins may be in part responsible for an elevation of portal vein pressure, in addition to and in conjunction with, any vascular spasm that may be present. Since thrombi are found in both lungs and liver in animals given incompatible blood or bacterial endotoxins,[4, 6, 9] it may be that both of the above mentioned mechanisms are in operation to produce shock in these experiments. The reason that thrombi are seldom seen in routine autopsies is that they are usually dissolved after a time by fibrinolytic enzymes.[4, 6] This also probably accounts for the transient nature of the shock produced in these experiments and the return of pulmonary pressure to normal after a time.

Summary and Conclusions

1. The immediate (reversible) shock resulting from the injection of amniotic fluid into dogs is prevented by prior heparinization of the animal.

2. Shock resulting from injection of incompatible blood is partially but not completely prevented by heparinization.

3. These observations point to the probability that intravascular coagulation may be a cause of shock.

4. Portal vein pressure is elevated in this type of shock while systemic vein pressure falls.

5. Pulmonary blood pressure is apparently elevated in this type of shock. There is an apparent increase in pulmonary resistance.

6. There is some evidence that shock may be due to a decreased cardiac output secondary to

a. Acute cor pulmonale. This may be due to intravascular thrombi in the lungs plus associated vascular spasm damming the flow of blood.

b. Decreased venous return to the heart. This may be due to thrombosis and associated vascular spasm in the small vessels of the liver with consequent damming of blood in the portal system.

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